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RELATION OF VITAMIN D AND INSULIN RESISTANCE IN TYPE 2 DIABETES MELLITUS

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Abstract

Background: It is worth noting that vitamin D deficiency is very common and may be associated with the pathogenesis of insulin-resistance-related diseases, including obesity and diabetes. Insulin resistance (IR) is the primary pathogenic factor, contributing to impaired glucose tolerance and diabetes complications. Vitamin D deficiency, linked to increase IR and metabolic syndrome, is prevalent in T2DM patients. Vitamin D (VD) may influence insulin sensitivity or pancreatic β-cell activity, thereby contributing to the development of Type 2 Diabetes Mellitus (T2DM). This review aims to provide molecular mechanisms showing how vitamin D deficiency may be involved in the insulin resistance formation. More recently, it was also shown that vitamin D prevents epigenetic alterations associated with insulin resistance and diabetes. The impact of vitamin D deficiency on the incidence of various diseases and its relationship with the progression of type 2 diabetes mellitus (T2DM) is still controversial. **Conclusion:** Although the relationship between vitamin D and insulin resistance in T2DM seems promising, more research is required to fully comprehend the underlying mechanisms and create therapeutic care guidelines that are supported by data. The potential for vitamin D to increase insulin sensitivity and diabetes management is great, but it must be treated cautiously and supported by more scientific evidence.

Keywords: Diabetes Mellitus (DM), Type 2 Diabetes Mellitus (T2DM), Insulin Resistance.

INTRODUCTION

Diabetes mellitus (DM) refers to a collection of metabolic diseases that cause peripheral insulin resistance (IR) and hyperglycemia as a result of relative or absolute insulin insufficiency [1]. Another name for type 2 diabetes mellitus (T2DM) is adult-onset diabetes. It affects 5-7% of people worldwide [1]. T2DM accounts for 90–95% of all diabetes types. It has been determined that low HDL cholesterol, high triglycerides, and hypertension are risk factors for type 2 diabetes [3]. Exercise, hypoglycemic medications, and dietary therapy are typically used to regulate the condition [1]. One important regulator of lipid and carbohydrate metabolism is insulin. Insulin is secreted by the pancreatic β-cells in response to an increase in blood glucose [2]. The main pathogenic component of type 2 diabetes (T2DM) is insulin resistance (IR), which is related to and contributes to the development of impaired glucose tolerance in T2DM as well as complications from diabetes [3]. Vitamin D (VD) is a steroid hormone that is soluble in fat. Bone health and calcium homeostasis are well-established domains in which it functions. Vitamin D deficiency is defined as less than 20 ng/mL, VD insufficiency as defined by levels between 21 and 29 ng/mL, normal VD level as defined over 30 ng/mL, and VD intoxication as defined over 150 ng/mL [5]. To enhance glycaemic control in T2DM patients or slow the progression of prediabetes to T2DM,

numerous randomised clinical trials with vitamin D have been carried out [4]. In particular, there seems to be a link between low vitamin D levels and an elevated risk of IR. Vitamin D supplementation is a promising avenue for preventing or treating insulin resistance. A significant improvement in glycated haemoglobin (HbA1c) level upon the correction of vitamin D deficiency is also linked to low vitamin D levels, beta-cell dysfunction, and insulin resistance. Deficit in vitamin D is linked to metabolic syndrome, increased insulin resistance, and decreased insulin production [6].

ADA Criteria (2023) for the diagnosis of diabetes

FPG level ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. *

Or

2-hour PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be carried out in accordance with WHO guidelines, using a glucose load equivalent to 75 g of anhydrous glucose dissolved in water*.

Or

A1C ≥ 6.5% (48 mmol/mol). To test for hyperglycemia or hyperglycaemic crisis, a random plasma glucose level of ≥200 mg/dL (11.1 mmol/L) should be performed in a laboratory using an NGSP-certified and standardized method.

Or

A patient with hyperglycemia or hyperglycaemic crises has a random plasma glucose level of ≥200 mg/dL (11.1 mmol/L). [7].

Insulin resistance as a risk factor for type 2 diabetes mellitus (T2DM)

Insulin resistance is required for the development of type 2 diabetes and can occur even when insulin production is adequate. Insulin resistance is a result of disruption in the insulin signalling system. Insulin is a key modulator of energy balance through the regulation of several enzymes and kinases during eating and fasting [2]. Insulin resistance is an early aberration that can be permanently rectified by improving β-cell function before the insulin-glucose feedback loop fails. Insulin resistance is linked to outcomes and cardiovascular disease as well being a risk factor for type 2 diabetes.

The most significant risk factors for type 2 diabetes include male sex, advancing age and obesity. Insulin resistance is common in people with the so-called metabolic syndrome, which includes dyslipidaemia, hypertension and dysglycemia in addition to visceral obesity. This syndrome has also been linked to hyperuricemia, arteriosclerosis, microalbuminuria, platelet hyper- aggregation, ant -fibrinolysis, sleep apnoea, and male hypogonadism. First-degree relatives of people with type 2 diabetes (T2DM) as well as women with a history of PCOS or GDM—both of which are characterised by a high insulin resistance—are also significantly more likely to develop T2DM. The question of whether chronic insulin resistance is a hereditary or acquired condition is raised by these conditions. Even the combination of all currently known diabetes-related genes adds relatively little to the prediction of type 2 diabetes based on gender, age, and body mass index, despite the fact that a family history of the diabetes increases the risk of the disease in the relatives. The incidence of type 2 diabetes is significantly reduced by interventions that improve insulin resistance,

highlighting the significant influence of lifestyle on the development of insulin resistance. Consequently, a number of lifestyle-related metabolic variables are linked to or predict insulin resistance and type 2 diabetes. These variables, which include plasma concentrations of nonesterified or free fatty acids (FFAs), serum triacylglyceride to-serum high-density lipoprotein (TAG/HDL-C), and ectopic fat content in the liver (hepatocellular lipid content, HCL) or skeletal muscle (intramyocellular TAGs), are primarily associated with lipid metabolism.

Furthermore, a major epidemiological investigation found that plasma concentrations of amino acids also predict type 2 diabetes (T2DM), with red meat eating ranking among the top predictors. Additionally, there's evidence that changes in cytokine secretion patterns, mostly from adipose tissue, and an increase in proinflammatory markers in the bloodstream such C-reactive protein could be predictive factors for T2DM and insulin resistance. Conversely, transforming growth factor-β1 (TGF-β1), growth differentiation factor-15 (GDF-15), and interleukin-1 receptor antagonist (IL-1RA) all have higher concentrations prior to the onset of type 2 diabetes (T2DM), indicating the presence of a compensatory, but ultimately ineffective, counter-regulation of proinflammatory stimuli. In contrast, adiponectin is the only anti-inflammatory cytokine with lower circulating levels. Insulin resistance may progressively impact some insulin-responsive tissues, such as skeletal muscle, liver, and adipose tissue, even though all metabolic and inflammation-related factors also circulate systemically and may have effects in several tissues at once [11].

Pathogenesis of T2DM

Insulin resistance is characterised by the target tissues' incapacity to react appropriately to the body's endogenous insulin releases, including skeletal muscle and adipose tissue. The pancreatic islets of Langerhans, which include b-cells, will produce and secrete insulin into the blood in a biphasic pattern in a normoglycemic person in response to an increase in blood glucose. Insulin is an anabolic hormone that promotes the synthesis of protein, lipids, and glycogen from glucose in order to construct tissues. Although this mechanism is compromised in people with type 2 diabetes, glucose transporters-4 (GLUT-4) are incharge of glucose uptake into tissues, which works to lower blood glucose to an ideal level between 3.9 and 5.8 mmol/L.

T2DM has a very complicated aetiology that involves numerous organs, tissues, routes, and hormones. As previously mentioned, the exact processes causing the reduction in insulin sensitivity remain unclear; yet, some have linked the reduction in insulin sensitivity seen in type 2 diabetes to hyperglycemia or "glucotoxicity." By increasing serine and threonine phosphorylation of the insulin receptor, which has an inhibitory effect, and further lowering tyrosine phosphorylation, hyperglycemia is hypothesised to aggravate insulin resistance. People with type 2 diabetes are thought to have a 50% reduction in insulin receptor autophosphorylation, hyperglycemia may play a role in this. Reactive oxygen species (ROS), which are advantageous at low concentrations but harmful at supra-physiological levels, have also been demonstrated to be produced in greater quantities in hyperglycemia. The activity of relevant antioxidant enzymes, such as glutathione reductase and superoxide dismutase (SOD), is decreased by hyperglycemia. These enzymes are crucial in neutralising ROS and may provide protection by reducing the low-grade inflammation that is typical of type 2 diabetes. Insulin resistance is also believed to be influenced by "lipotoxicity" in addition to "glucotoxicity." A high quantity of free fatty acids (FFA) in

the bloodstream brought on by a decreased inhibition of hormone-sensitive lipase (HSL) is referred to as lipotoxicity. Insulin normally blocks HSL, which prevents lipolysis; in those who are resistant to insulin, this process is less effective. Obesity and increased adiposity, especially in the visceral area, are concerning because of the rise in lipolysis and circulating FFA that follows. Serine phosphorylation of the insulin receptor, which again reduces the activity of the insulin signalling pathway, is thought to be the mechanism by which FFA cause insulin resistance. For the insulin signalling pathway to be activated, the insulin receptor on tyrosine amino acids must be phosphorylated. If this is not done, GLUT-4 will not translocate, and the absorption of glucose into tissues will be reduced, which can result in T2DM or persistent hyperglycemia. Increased cytokine production may be a factor in the prevalence of insulin resistance and type 2 diabetes in this population, as evidenced by the discovery of elevated TNF-a levels in insulin-resistant obese people without T2DM. Despite the fact that not everyone who is insulin resistant goes on to develop type 2 diabetes, it is crucial to recognise the key role insulin resistance plays in the pathophysiology of T2DM **[8]**.

Pathophysiology of Insulin Resistance

The metabolism of fat and carbohydrate is significantly regulated by insulin. An elevation in blood glucose levels triggers the release of insulin from the pancreatic β-cells. Fructose-2,6-P2 (F-2,6-P2) is produced by the pancreatic β-cells upon glucose entry through the glucose transporter 2 (GLUT2). As F-2,6-P2 enters the glycolytic route and the tricarboxylic acid cycle, the amount of ATP increases. Insulin is secreted when ATP levels are elevated because they inhibit the ATP-sensitive K+ channel, which depolarises the membrane and activates L-type voltage-operated channels, which produce localised Ca2+ pulses [2]. The physiologic effects of insulin in the insulin-responsive tissues—mainly the liver, adipose tissue, and skeletal muscle—cause a person to be sensitive to the hormone. The general definition of impaired insulin sensitivity, also known as insulin resistance, is decreased glucose clearance in skeletal muscle, impaired liver suppression of glucose production, decreased rates of lipolysis in adipose tissue, or a decreased collective effect on the body's ability to eliminate glucose [11].

Vitamin D Synthesis and Metabolism

When exposed to sunshine, the body can also synthesize vitamin D. The two active forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The primary circulating and cutaneously synthesised form of vitamin D, 25(OH)D, is created in the liver by activating VD, which is then transferred to the adipose tissues for storage. Following this, the kidneys convert it to 1,25-dihydroxyvitamin D, the active form that travels throughout the body and attaches to vitamin D receptors, a transcription factor, in different tissues [4]. Insulin secretion and pancreatic β-cells are impacted by the active metabolite 1,25-dihydroxyvitamin D3. It might potentially influence insulin sensitivity via a number of other channels **[2]**.

Type 2 Diabetes and Vitamin D

Hypovitaminosis D may be the source of this seasonal shift in glycaemic control, which is worse in these people, as type 2 diabetes is more frequent in the winter when there is less sunlight. This suggests a possible link between lowered vitamin D levels and type 2 diabetes. The recent study that looked at the impact of calcium plus vitamin D supplementation on the incidence of drug-treated diabetes in postmenopausal women

came to the conclusion that, over the course of a seven-year follow-up, calcium plus vitamin D3 supplementation did not lower the risk of developing diabetes. An extensive prospective observational cohort is the Nurses' Health Study. The study discovered that women who consumed the calcium and vitamin D (>1200 mg and > 800 IU daily, respectively) were 33% less likely to experience an incident case of type 2 diabetes mellitus than those who consumed the least (< 600 mg and < 400 IU daily, respectively). Another large Finnish cohort study found an inverse link between type 2 diabetes risk and serum 25(OH)D3. Nevertheless, it was unable to determine from these investigations whether the effects were caused by insulin resistance or by the impact of vitamin D insufficiency on beta-cell function. Numerous studies have suggested that vitamin D plays a direct role in the regulation of the endocrine pancreas's function, specifically in relation to the beta-cells. Beta-cells have receptors for 1,25(OH)2D3, but they also include calbindin-D28k, a protein that binds calcium in response to vitamin D, which is the effector portion of the VD pathway. Long believed to be a risk factor for developing glucose intolerance. The deficiency of vitamin D can result from either a relative VD resistance or a VD shortage. For example, long-term VD treatment of osteomalacia improves glucose tolerance and enhances insulin secretion. Moreover, it has been proposed that hyperinsulinemia is linked to higher bone mineral density in both diabetic and non-diabetic people. Furthermore, vitamin D treatment has not been shown to improve glucose tolerance in those who do not have a vitamin D deficiency [8].

Insulin resistance and vitamin D

1,25-dihydroxyvitamin D is vital for maintaining glucose homeostasis. It not only increases the target cells' (adipose tissue, skeletal muscle, and liver) sensitivity to insulin, but it also strengthens and improves β-cell activity. Furthermore, by acting directly on β-cells and indirectly on various immune cells such as dendritic cells, inflammatory macrophages, and various T cells, β-cells are protected from damaging immune attacks by 1,25-dihydroxy vitamin D. Macrophages, dendritic cells, T lymphocytes, and B lymphocytes can all produce 1,25-dihydroxy vitamin D, all of which are involved in the control of peripheral immunological responses [8]. Fasting Insulin (IU/mL) and glucose (mmol/mL) measurements were used to calculate the HOMA-IR, which is divided by factor 22.5. The plasma 25(OH)D was determined by chemiluminescence assay [9].

Vitamin D—Other Disorders Associated with Insulin Resistance:

Insulin resistance has a role in the pathogenesis of polycystic ovarian syndrome, gout, and both classic and nonclassic adrenal hyperplasia. Many times, type 2 diabetes coexists with these disorders. Research has demonstrated that insulin-sensitizing medications, such as vitamin D replacement or supplementation, improve these situations **[10]**.

DISCUSSION

Overall, observational longitudinal studies have demonstrated a negative correlation between the onset of type 2 diabetes and the level of vitamin D 25(OH)D or intake as stated by the individual. There could be several reasons for the decline in the connection between vitamin D and T2DM that has been seen in observational research and recorded in randomised controlled clinical trials (RCTs). Numerous factors may complicate of VD levels have an inverse connection with glycaemic

outcomes. Overall, the evidence currently available does not support the claim that raising the concentration of 25(OH)D can ameliorate T2DM. To investigate the theory that vitamin D deficiency directly contributes to the pathophysiology of type 2 diabetes, large trials in well-defined populations (e.g., pre-diabetes, early type 2 diabetes, and Whites versus non-Whites) are required to confirm a potential beneficial of vitamin D effect on T2DM [12].

The above findings have shown that in T2DM patients, vitamin D treatment significantly reduced blood FPG (fasting plasma glucose), insulin, and HOMA-IR. The connection between basal 25(OH) D concentration and final FPG was inverse. When vitamin D concentration was between 40 and 60 ng/ml (100 and 150 nmol/l), insulin resistance was pronounced at lower but with higher vitamin D concentrations, insulin resistance was unaffected. Many previous published research work have shown that vitamin D treatment to T2DM patients reduces their insulin resistance. For instance, Inzucchi demonstrated a 60% increase in insulin sensitivity by raising the range of the serum 25(OH)D concentration, which is 10–30 ng/ml, (25 to 75 nmol/l), which resulted in 54% and 13% of metformin or troglitazone, respectively. It appears that vitamin D raises calcium levels in cells, which in turn promotes higher muscular uptake of glucose. Additionally, vitamin D controls nuclear PPAR (peroxisome proliferative activated receptor), which is crucial for insulin sensitivity. Increases in inflammation are linked to vitamin D deficiency. Insulin resistance-related proinflammatory cytokines, including interleukins, IL-1, IL-6, and TNF-a, are less expressed when vitamin D is present. It also inhibits the action of NF-Kb (Nuclear factor) [13].

This could suggest that vitamin D3 acts as a preventive measure against the development of insulin resistance. This could be the case since insulin resistance is mostly caused by inflammation, which vitamin D3 can effectively prevent from happening via upregulating MAP kinase, controlling the NF-kB signalling pathway, controlling cytokine levels, and controlling the prostaglandin pathway, Vitamin D3 can prevent inflammatory reactions from occurring and thereby reduce insulin resistance. While few studies have indicated that moderate alcohol consumption is beneficial to avoid insulin resistance, it is crucial to remember that this is not the ideal strategy for preventing insulin resistance. It appears that a balanced diet is a better strategy for preventing insulin resistance.

A subgroup analysis revealed that there were racial differences in the link between vitamin D3 and insulin resistance (P=0.008). This demonstrates how different racial groups have different relationships between insulin resistance and vitamin D3 levels. Research has demonstrated that UV radiation inhibits the process by which dark-skinned people synthesis D3. [15]. This study found that taking vitamin D3 reduces the chance of developing insulin resistance by 0.82-fold for every additional unit of vitamin intake. This could indicate that vitamin D3 protects against the development of insulin resistance. This could be because vitamin D3 effectively inhibits the onset of inflammation, and inflammation is the primary factor causing insulin resistance. In this work, we discovered that vitamin D3 is linked to insulin resistance, confirming its function in the aetiology of diabetes. Currently, research indicates a linear link between vitamin D3 and insulin resistance. Thus, maintaining increased vitamin D3 levels within a particular range is crucial to prevent insulin resistance, and this conclusion provides a recommendation for clinical management.[15]

CONCLUSION

The existing literature revels positive relationship between vitamin D and insulin resistance in Type 2 Diabetes Mellitus. Evidence suggests that optimal VD level improve insulin sensitivity and glycaemic management in patients with Type 2 diabetes. VD appears to regulate insulin output and reduce systemic inflammation, both of which are critical in the management of diabetes mellitus. However, more research is needed to completely understand the mechanisms involved and to determine the ideal vitamin D doses for therapeutic purposes. An increasing amount of research indicates that vitamin D supplementation may be a helpful addition to existing treatments for Type 2 Diabetes Mellitus.

References

1) Jangid H, Chaturvedi S, Khinchi MP. An Overview on Diabetes Mellitus. An Overview on Diabetis Mellitus Asian Journal of Pharmaceutical Research and Development. 2017;5(3):1–11.

2) Szymczak-Pajor I, Śliwińska A. Analysis of association between vitamin D deficiency and insulin resistance. Nutrients. 2019;11(4):794.

3) Lei X, Zhou Q, Wang Y, Fu S, Li Z, Chen Q. Serum and supplemental vitamin D levels and insulin resistance in T2DM populations: a meta-analysis and systematic review. Sci Rep.2023;13(1):12343.

4) Abugoukh TM, Al Sharaby A, Elshaikh AO, Joda M, Madni A, Ahmed I, et al. Does vitamin D have a role in diabetes? Cureus. 2022; 14(10):e30432.

5) İnci H, İnci F. The relationship between serum vitamin D level and Type 2 Diabetes Mellitus. Med Sci Discov.2021;8(2):79–85.

6) Khudayar M, Nadeem A, Lodi MN, Rehman K, Jawaid SI, Mehboob A, et al. The association between deficiency of vitamin D and T2DM. Cureus. 2022; 14(2):e22221.

7) ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes—2023. Diabetes Care. 2023; 4(1):S19–40.

8) Moreira TS, Hamadeh MJ. The role of vitamin D deficiency in the pathogenesis of type 2 diabetes mellitus. E Spen Eur E J Clin Nutr Metab. 2010;5(4):155-165.

9) Hammel MC, Stein R, Kratzsch J, Vogel M, Eckert AJ, Triatin RD, et al. Fasting indices of glucose-insulin-metabolism across life span and prediction of glycemic deterioration in children with obesity from new diagnostic cut-offs. Lancet Reg Health Eur. 2023;30(100652).

10) Sacerdote A, Dave P, Lokshin V, Bahtiyar G. Type 2 diabetes mellitus, insulin resistance, and vitamin D. Curr Diab Rep. 2019;19(10):101.

11) Roden M, Petersen K, Shulman G. Insulin Resistance in Type 2 Diabetes. In: Textbook of Diabetes. 2017; 5:455-56.

12) Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. Eur J Clin Nutr. 2011;65(9):1005–15.

13) Pilz S, Kienreich K, Rutters F, de Jongh R, van Ballegooijen AJ, Grübler M, et al. Role of vitamin D in the development of insulin resistance and type 2 diabetes. Curr Diab Rep. 2013;13(2):261–70.

14) Talaei A, Mohamadi M, Adgi Z. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. Diabetol Metab Syndr. 2013;5(1):8.

15) Xu Z, Gong R, Luo G, Wang M, Li D, Chen Y, et al. Association between vitamin D3 levels and insulin resistance: a large sample cross-sectional study. Sci Rep. 2022;12(1):119.